An essential aspect of research on schizophrenia is ensuring that worthwhile scientific studies are done in a way that does not place vulnerable individuals at unreasonable risk. It is important to educate researchers, advocates, potential participants, reviewers, IRBs, and the general public about ethical principles and controversial issues as they impact research on schizophrenia. Federal regulations mandate IRB consideration of “the special problems of research involving... mentally disabled persons...” (45CFR46.111a3). In recent years, there has been a greater focus on subject monitoring to improve safeguards and minimize risks. The process of informed consent is also going through a process of evolution, in order to help ensure that participants are as aware as possible of key aspects of a study, including risks, benefits, alternatives, purpose and design, etc. We focus here on a few of the issues that are current, are relevant to schizophrenia research, and merit additional empirical study. They include medication discontinuation and placebo control designs, compensation for participation, and capacity to consent.

**Key words:** research ethics/schizophrenia/placebo/consent capacity

**Introduction**

Federal regulations (45CFR46.111) mandate IRB consideration of “the special problems of research involving... mentally disabled persons...,” and a criterion for IRB approval is that when subjects “are likely to be vulnerable to coercion or undue influence, such as... mentally disabled persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.” The Regulations further note (45CFR46.116) that information given to the subject or representative “shall be in language understandable to the subject ....” Beyond that, there is little of specific relevance to schizophrenia research in the “Common Rule” provisions, but naturally there are various interpretations and opinions about how these rules should apply. Some have advocated adding Special Subpart Protections to the Regulations to more specifically cover people with mental disorders, while others have expressed concerns about such efforts. We will be hearing more about this topic in the future, but it will not be a subject of the current discussion.

An essential aspect of research on schizophrenia is ensuring that worthwhile scientific studies are done in a way that does not place vulnerable individuals at unreasonable risk. It is important to educate researchers, advocates, potential participants, reviewers, IRBs, and the general public about ethical principles and controversial issues as they impact research on schizophrenia. Unfortunately, until recently there has been little effort focused on addressing empirical questions relevant to these issues. The NIH has emphasized the importance of research on ethical issues such as informed consent, and supports an increasing number of studies on such topics.

In recent years, there has been a greater focus on subject monitoring to improve safeguards and minimize risks. Data and safety monitoring plans are now commonly made explicit in clinical trials, and independent Boards may meet regularly to assess study progress, adverse events, reporting requirements, etc. The process of informed consent is also going through a process of evolution, in order to help ensure that participants are as aware as possible of key aspects of a study, including risks, benefits, alternatives, purpose and design, etc. Below we will focus specifically on a few of the issues that are current, are relevant to schizophrenia research, and merit additional empirical study. They include medication discontinuation and placebo control designs, compensation for participation, and capacity to consent.

**Drug Discontinuation**

One especially controversial schizophrenia research design involves either stopping or delaying treatment, often for the purpose of biological studies such as PET scans or neurochemical assays. Delaying treatment, especially for individuals who have severe disorders (such...
as schizophrenia), which may benefit from immediate treatment, may create a dilemma. Consent documents now generally include (under “alternatives”) the option to begin treatment immediately, and not to delay or defer (for the purpose of participating in a research study) medication and/or psychotherapy. Individuals must be informed that participation is voluntary and that they can withdraw at any time. They should also know that their symptoms may well worsen, and that suicidal ideation or other dangerous situations may begin to develop. In such situations, they need to know whom to contact.

Investigators need to set up an adequate safety net to ensure appropriate clinical assessment, and monitoring sufficient to detect and respond to emerging problems. The discontinuation design may be used for selected subject groups who have not benefited substantially from treatment, have experienced problematic side effects, or have chosen (independent of the study) to remain off (or discontinue) treatment.

Another controversial type of drug discontinuation research involves prolonged discontinuation of effective treatment. It has been noted that starting patients on medications and leaving them on for many years, adding additional medications as additional symptoms or side effects occur, can create numerous clinical problems. Clearly we would like to know from a scientific perspective, and patients want to know from side effects and other perspectives, how long they “need to take” a given medication or remain in psychotherapy. In many situations, we do not yet know the answers to these questions.

Unfortunately, discontinuing treatment of people with severe disorders such as schizophrenia may lead to dramatic symptom exacerbations and clinical complications. While it is important to learn how long people need to remain on medications, studies have shown that for many psychiatric disorders like schizophrenia, prolonged treatment is often necessary because of its generally chronic and/or recurring nature. Removal of such treatments naturally will raise some concerns.

If individuals are being withdrawn from medications to which they are currently responding well, the risks/benefits/alternatives to the discontinuation phase should be made clear in the withdrawal phase consent document. Medication withdrawal protocols may involve substantial risks (relapse, hospitalization, suicidal ideation, or problems at home, school, work, etc.). Since these designs are not generally considered to present the prospect of direct benefit (other than diminishing side effects), strong ethical justification is essential. As noted above, selection of subjects who have not benefited from treatment, have had major side effects, or have chosen independently to stop treatment would minimize some of the ethical concerns (but may raise some scientific concerns about generalizability).

The risk of relapse, consideration of alternative treatments that may be more acceptable, and monitoring safeguards must all be considered by IRBs and investigators, and reflected in consent documents. The selection of potential subjects must be carefully considered, along with the availability of treatment for those who worsen clinically and require rescue medication. One alternative is to remain on a treatment that currently appears to be effective. This might be the case even if the treatment in a clinical trial was a placebo. In fact, continuing individual responders on placebo, and comparing them with responders on active medication, may help determine whether there is a point at which a “separation” occurs; i.e., if the placebo effect seems to diminish over time. This could lead to better empirical data on how long a placebo arm should be continued in various trials.

Financial Incentives/Compensation

In decades past, it was relatively unusual to pay participants in clinical research, but outlooks have evolved considerably on this subject. For instance, the time of an individual with a mental disorder like schizophrenia is no less valuable than that of anyone else, and compensation is now generally provided to patients if it is to be provided to controls. This was discussed cogently at the December 2001 PRIM&R meeting in Boston. Of course, there are concerns that paying participants large sums of money could be an “undue inducement.” That is, payments should not cause individuals to place themselves at significant risk, which they would not otherwise accept. It has also been pointed out that financial compensation should not be listed in consent documents as a “benefit,” since it is not to be balanced against the risks of a study. We generally want to avoid individuals balancing how much risk of harm to their health they should undertake in order to receive certain compensation. This is especially true given that people with schizophrenia are more likely to be socio-economically disadvantaged.

Reimbursing individuals for their time, travel, etc., at a reasonable rate is certainly appropriate, and we are seeing this much more commonly today. It has, in fact, been pointed out that there may be an unexpected benefit from reimbursing individuals’ costs related to participation in clinical trials. It has been well demonstrated that individuals in a research protocol, despite being told in the consent process that they are being assigned randomly to a treatment group in a clinical trial, often believe that they are getting what the (research) doctor thinks will help them most. This is the “therapeutic misconception,” which has been described by Paul Appelbaum and colleagues. In clinical practice, we do not pay individuals to come in for their appointments or take medications to treat their condition, and some have speculated that such payments during clinical trials may make clearer to participants that this is not individualized treatment. This certainly seems worthy of empirical study. Another interesting question is the extent to which financial compensation may become an undue inducement such that
individuals attempt to enter a study denying exclusion criteria, or try to continue in a study despite suffering severe clinical symptoms.

The above issues are clearly related to the more generic question of why people participate in research in the first place. Certainly schizophrenia and altruism are not mutually exclusive. Many mental disorders are familial, and one should not be surprised that a person wants to help other family members, or society in general, now or in the future. Data have already been gathered by Laura Roberts and others, making clear that altruism (not just possible direct benefit) is an important determinant of research participation. Perhaps some individuals in our society do not believe in altruism and would not participate in a study that did not offer them direct benefit, but to assume that this holds widely for individuals with mental disorders seems completely unwarranted, if not insulting.

**Placebo Controls**

Most researchers consider placebo control groups extraordinarily valuable under certain circumstances. In many cases, we would still be using relatively worthless and/or dangerous treatments had we agreed to abandon studies with placebo arms. If we do not know whether a treatment works, it seems ethically questionable to provide it, especially if it entails problematic side effects. On the other hand, the use of a placebo control needs to be well justified (vs. comparison between experimental and standard treatment arms). Clearly, if permanent or severe progression of disease will occur in the absence of treatment, a placebo control arm is not going to be considered appropriate or justified.

A related issue is the use of planned debriefing, so that at the end of an acute trial, participants are told what they were receiving and how well their symptoms appeared to respond. Delaying debriefing until the entire study is complete and the blind formally broken may not be considered acceptable by IRBs. In particular, participants who were on placebo are generally offered active treatment after an acute trial.

Debriefing helps people who didn’t respond to a medication avoid that ineffective treatment in the future, and may help them find better alternatives. It also allows those who did respond to seek continuation of the effective treatment, and it is becoming more common for research teams to offer such treatment free of charge (for a period at least as long as the acute trial). To preserve the blind, an independent clinician not part of the research team may conduct the debriefing. After that, there is typically a treatment referral to an available clinician.

**Capacity to Consent**

Individuals in a wide variety of situations may have impaired decision-making capacity, for example, at times of great stress. Impaired capacity is not limited to individuals with severe mental disorders like schizophrenia, and such individuals should not be presumed to be decisionally impaired. Some research questions may only be answered by research that involves persons with impaired decision-making capacity. Precluding such research could have very negative effects, as the most severely impaired individuals have the greatest need for the benefits of research on etiology and treatment. Limiting research to the least-impaired individuals would hamper research on the underlying causes and potential therapies of schizophrenia. Not all research will directly benefit the individual participant, but it may offer future benefits to others who have or will develop the condition or disorder. For example, genetic studies, biochemical measures, or other “non-therapeutic” approaches may greatly benefit subsequent generations.

Unlike research involving children, prisoners, pregnant women, and fetuses, no additional Department of Health and Human Services (DHHS) regulations specifically govern research involving persons who are cognitively impaired. While limited decision-making capacity should not necessarily prevent participation in research, it is important to keep in mind that additional scrutiny by IRBs and researchers is warranted for research involving this population.

An individual’s capacities, impairments, wishes, and needs must be taken into account in developing practical and ethical approaches to evaluate their potential participation in clinical studies. Several research groups are developing and testing valid and practical methods to assess capacity to consent, and NIMH will continue to support research addressing these issues. At the May 2005 APA meeting, there were several excellent presentations on this topic. A clear understanding of the implications of various cognitive impairments, along with a careful consideration of proposed clinical research methodology, is needed.

A “sliding scale” involving assessment of risks, benefits, and capacity to consent should guide the IRB’s decisions regarding additional safeguards. Many strategies are available for investigators as they develop their research protocols, and for IRB members as they evaluate them. In considering increasing levels of risk and/or impairment, investigators should be creative in choosing appropriate protections, seeking strategies used successfully in similar situations.

When reviewing greater than minimal risk research involving individuals with questionable capacity to consent, IRBs should discuss and document the potential value of an independent monitor. A monitor can be appointed to be present when investigators invite individuals with impaired decision-making capacity to participate in a research study. The consent process should be visible throughout, and IRBs have a right to observe recruitment, assessment, the informed consent process,
and debriefing of research participants (and/or their family/surrogates).

Where permitted by law, individuals with impaired capacity may have a family member or other legally authorized representative serve as a surrogate for research decisions, with this role documented during the consent process. Unfortunately, it may be unclear what is permitted by law. Many states have statutes or regulations defining who may serve as surrogates in the context of medical practice, but it is often unclear whether these laws also cover research. OHRP has opined that if a state law permits a certain type of surrogate to authorize a certain type of procedure in the medical practice context, then that same type of surrogate would have authority to authorize similar procedures in the research context.

Surrogates should be informed of the risks, benefits, and alternatives to the research when they are deciding whether to give permission for an individual to participate. Whenever possible, surrogates should make such decisions based on substituted judgment, reflecting the views of the individual as expressed while decisionally capable. Best interest standards should be used if the values of the individual are not known. It is important that surrogates receive some education about their own role and the cognitive and health status of the research participant, as well as about the study in which the participant may be involved.

Because informed consent is an ongoing process throughout the course of the protocol, assessing and enhancing comprehension at each stage is essential. Summaries of important information about key elements of a study may be useful, especially when provided on a regular basis, such as at each research assessment/monitoring session. Questions from potential participants and family members should be encouraged, and handouts of frequently asked questions and answers regarding specific human subject protections can be prepared. Communication between members of the research team and participants and their families/surrogates is key to successful research participation.

Conclusion

There are a great number of ethical questions related to schizophrenia research, and the sooner these are addressed in an empirical manner, the better. Improving consent capacity (and its assessment) is an area of very promising development. We should also acknowledge that many important scientific questions remain unanswered because we cannot yet conduct ethically acceptable studies that will provide valid answers. Advances in research design, and application of basic behavioral and neuroscience findings to the clinical problems of schizophrenia, may greatly improve risk/benefit considerations in such research.

While the underlying problems of schizophrenia have remained relatively constant over the years, the treatments available, and the clinical problems associated with newer treatments, have changed considerably. Likewise, the basic ethical principles of the Belmont Report\textsuperscript{13} and the Human Subject Protections Regulations (45CFR46)\textsuperscript{1} have been in existence for some time, but the way in which these are applied to clinical research issues has also been evolving. The work described in this issue of *Schizophrenia Bulletin* makes good use of recent interpretations and applications of the science and ethics advances to improve the lives of people with schizophrenia.

References


2. Carpenter WT, Schooler NR, Kane J. The rationale and ethics of medication-free research in schizophrenia. Arch Gen Psychiatry. 1997;54:401–407.


